Highly correlated model-based testing of insulin sensitivity – initial results for a proposed low-intensity test

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Introduction

Insulin resistance (IR) is a major risk factor in the pathogenesis of type 2 Diabetes and cardiovascular disease. A simple, high resolution assessment of IR would enable earlier diagnosis and more frequent monitoring of intervention effects. Current assessments are either too intensive for clinical settings (Euglycemic Clamp, IVGTT) or have too low resolution (HOMA).

Methods

A model-based insulin sensitivity metric (S_I) is validated on N=146 Euglycemic-Hyperinsulinemic Clamps during transient state. A novel, clinically useful test protocol is designed with: physiological dosing, short duration (<1hour), simple protocol, low cost, repeatability and high correlation to the clamp. Model-based S_I is assessed from low dose IV injections (10g glucose, 1U insulin) using glucose, insulin and C-peptide measurements in a <60 minute test. Accuracy and repeatability are assessed with Monte Carlo analysis on the virtual clamp cohort (N=146) and in pilot clinical trials on NIDDM, obese and lean subjects (N=6).

Results

Correlation between S_I and clamp ISI is r=0.97 in transient state. Insulin sensitivity from Monte Carlo analysis has a coefficient of variation (CV) of CV_{SI}=4.5% (90%CI: 3.8% - 5.7%), slightly higher than clamp ISI (CV_{ISI}=3.3% (90%CI: 3.0% - 4.0%)) and significantly lower than HOMA (CV_{HOMA}=10.0% (90%CI: 9.1% - 10.8%)). Pilot clinical trials show a high-resolution, 7x range in S_I between NIDDM and healthy subjects, and provide initial confirmation of the simulated test repeatability.

Conclusions

The proposed protocol is simple, cost effective, repeatable and highly correlated to the gold-standard clamp. Early clinical results match simulated accuracy and performance and provide high resolution. The protocol can be readily computationally engineered to a less intense, equally high resolution sub-30 minute version.